Pramipexole-containing dissolving microarray patches for the treatment of Parkinson's disease

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INTRODUCTION

Pramipexole (PRA) is a non-ergot dopamine agonist indicated to treat Parkinson's disease. PRA is currently available in tablet form with a maximum daily dose of 3.3mg (expressed in terms of PRA base) [1]. Due to the disease, patients usually experience dysphagia and gut motility issues, rendering oral preparations undesirable [2]. Dissolving microneedle array patches (MAP) can alleviate these issues. PRA base and its corresponding salt can be formulated in different ways to tailor the drug release kinetics from the MAP. PRA salt can be formulated with rapidly dissolving polymers with the aim of providing immediate release and PRA base can be formulated with a biodegradable polymer, poly(lactic-co-glycolic acid) (PLGA), with the aim of sustaining PRA release.

METHODS

PRA BASE

1. PRA base and PLGA (LA:GA 75:25, viscosity 0.8-1.0 dL/g) were dissolved in DMSO, with nile red added for staining purposes.
2. Followed casting process outlined below with steps 1 - 3 repeated for multiple casting layers.
3. MAPs underwent a needle height reduction test outlined below [3].

PRA SALT

1. PRA salt was mixed with 20% poly(vinylpyrrolidone) (PVP) 58kDa and 15% poly(vinyl alcohol) (PVA) 9-10kDa.
2. Followed casting process outlined below.
3. MAPs underwent a needle height reduction test outlined below [3].

Casting process:

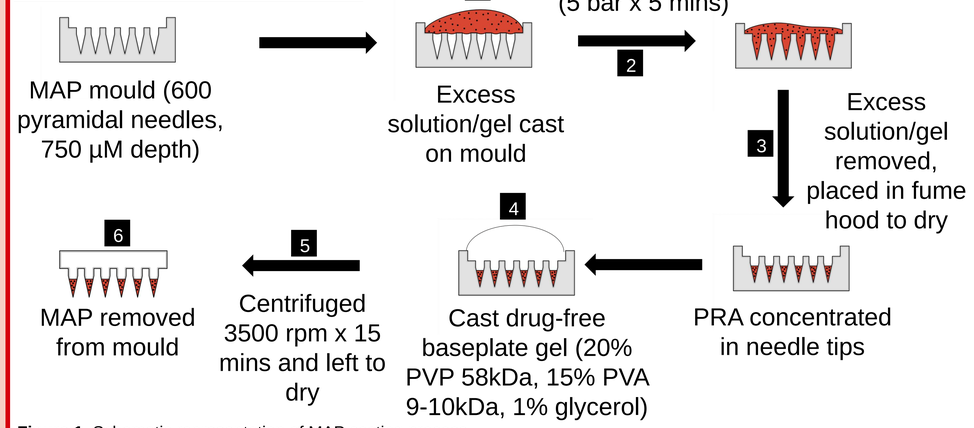

Figure 1. Schematic representation of MAP casting process

Needle height reduction test:

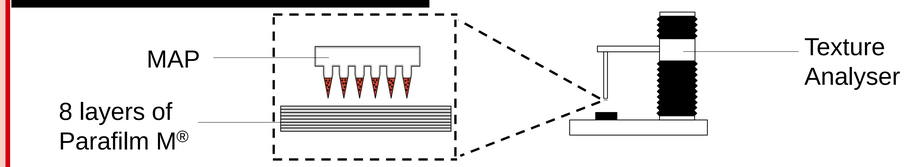

Figure 2. Schematic representation of the needle height reduction test using the Texture Analyser

1. MAP compressed at 32N into Parafilm M® for 30s
2. Parafilm M® layers unfolded and holes in each layer counted
3. Calculation of needle height reduction

RESULTS AND DISCUSSION

PRA BASE

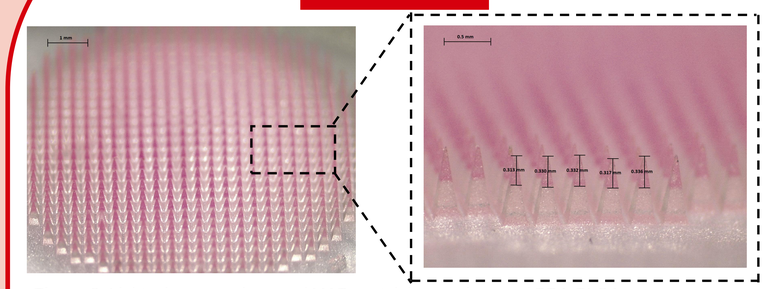

Figure 3. Light microscope image of MAP containing two layers of PRA-PLGA

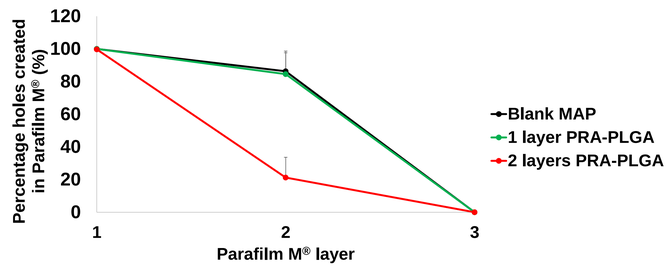

Figure 4. Percentage holes created in skin insertion model (means + SD, n=6)

Table 1. Characteristics of PRA-PLGA MAPs (means ± SD, n=6)

Number of PRA-PLGA casting layers	% height reduction after needle height reduction test	Height of PLGA tip (µM)
Blank MAP, PLGA only	5.12 ± 2.76	225.69 ± 12.45
1	4.24 ± 3.40	239.92 ± 15.62
2	6.98 ± 5.33	298.53 ± 17.79

- It was evident that PLGA was concentrated in the needle tips, resulting in a uniform distribution throughout the MAP.
- The height of the PLGA tips for one and two layer castings was 239.92 ± 15.62 µM and 298.53 ± 17.79 µM, respectively. This represents 32.0% and 39.8% of the total needle height, respectively.

PRA SALT

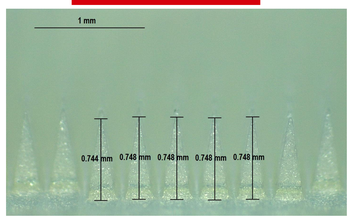

Figure 5. Light microscope image of MAP formed from casting gel containing 20% PRA salt

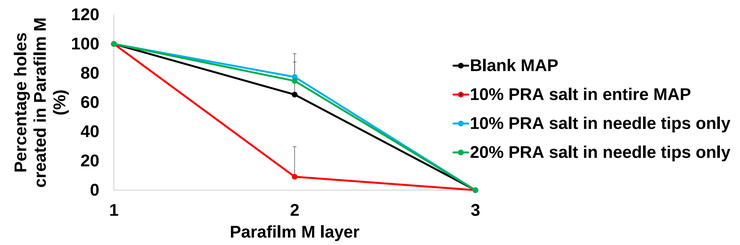

Figure 6. Percentage holes created in skin insertion model (means + SD, n=6)

Table 2. Characteristics of PRA salt MAPs (means ± SD, n=6)

Composition of MAP aqueous blend in terms of PRA salt	% height reduction after needle height reduction test	Drug content in terms of PRA base (mg)	Drug content in terms of PRA salt and base together (mg)
Blank MAP	2.95 ± 2.17	N/A	N/A
10% salt in entire MAP	15.42 ± 6.38	15.01 ± 2.53	21.43 ± 3.61
10% salt in needle tips only	2.34 ± 2.91	0.70 ± 0.05	1 ± 0.07
20% salt in needle tips only	16.49 ± 8.80	1.40 ± 0.19	2 ± 0.27

- Initially, PRA salt was incorporated into the entire MAP, including the baseplate. This resulted in needles with a high percentage height reduction and variable drug content. However, it shows the potential of MAPs to load a high amount of drug.
- 75% of needles in MAPs formed from casting gels containing 10% and 20% PRA salt were capable of penetrating through the 2nd layer of Parafilm M®.

CONCLUSION AND FUTURE WORK

This work has proven that PRA base and salt can be successfully formulated into MAPs using a variety of polymers. Future work will focus on *in vitro* permeation of PRA salt as well as permeation and skin deposition of PRA base using Franz cells.

REFERENCES

[1] National Institute for Health and Care Excellence. Parkinson's disease. 2017; Available from: https://bnf.nice.org.uk/treatment-summary/parkinsons-disease.html.
[2] Suttrup, I. and T. Warnecke, Dysphagia in parkinson's disease. *Dysphagia*, 2016. **31**(1): p. 24-32.
[3] Larrañeta, E., et al., A proposed model membrane and test method for microneedle insertion studies. *Int J Pharm*, 2014. **472**(1-2): p. 65-73.

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